Sera and Bacterial Products," Geneva, League of Nations Health Organization, 1929.

(13) Cockburn, W.C., "Field Trials in the Evaluation of Vaccines," *American Journal of Public Health*, 4/:819–825, 195/.

Labeling

Review of the labeling of products submitted to the Panel on Bacterial Vaccines and Toxoids identified a number of deficient areas in which, in the judgement of the Panel, substantial improvement should be made. The following generic comments on the subject of labeling highlight the view of the Panel on what constitutes adequate labeling, and provides a standard such that all labeling can be brought to an optimal level.

General Comments

Labeling should meet the following general criteria:

The labeling should be written in clear English. In many instances, current labeling is written with very complex sentence structure. There is very often marked ambiguity of meaning. In some instances, even Panel members charged with reviewing the subject were unable to determine the precise meaning of statements in the package insert; the physician who may be expected to give the labeling little more than a cursory reading therefore may often receive inadequate guidance.

Labeling should ordinarily contain information in the following format and order:

The labeling should be easily legible and printed in such a fashion as to attract, rather than to repel or discourage, the reader. Much of the present labeling is printed in type so small as to discourage all but the most determined reader.

The labeling should contain a summary of the essential scientific information the physician needs to use the bacterial vaccine or toxoid safely and effectively in the care of patients. It shoud be informative, accurate, and nonpromotional in tone.

Labeling should be reviewed and revised as necessary at intervals of no more than every 2 years. The date of last revision should be clearly identified in the label. Although the area of bacterial vaccines and toxoids has not been marked by rapid and dramatic advances resulting from medical research, immunization practices do evolve gradually with time and in the light of new data or circumstances. Many of the recommendations contained in the labeling of products currently on the market are out of step with current practice and recommendations. Bibliographic citations should similarly be revised and updated at intervals of no more than every 2 years.

Description
Clinical Pharmacology/Biological Activity
Indications and Usage
Contraindications
Warnings
Precautions
Adverse Reactions
Overdosage
Dosage and Administration
How Supplied

The Panel has reviewed and concurs with the proposed format changes as described in the statement on "Labeling of Prescription Drugs Used in Man" (21 CFR Part 200), previously circulated by the Food and Drug Administration. The following comments presume the adoption of these new standards, follow the same recommended format, and reflect the Panel's particular concerns in the labeling of bacterial vaccines and toxoids.

Description

This should be a concise statement of the method of preparation of the product, the characteristics of strain or species used, the scientific name of the bacterium, noting the specific strain if important, the process used, the potency standard that has been met, the antigenic content of the product, the stabilizers and preservatives included, and the suspending menstruum. Terms such as "purified" and "refined" are more promotional than scientifically meaningful. An accurate statement of the precise process that is used would be considerably more meaningful.

Clinical Pharmacology/Biological Activity

This section should contain a concise factual summary of the immunological response to the product in terms of immunity, antibodies, or other parameters. Specific points to be covered, when applicable, include: The proportion of individuals in which antibody will be produced, the number of doses required to produce satisfactory levels of antibody, techniques and reliability of antibody measurements, the time at which antibody is detectable, peak antibody levels to be expected, expected decay of antibody titers, and the degree and duration of protection to be expected. Concise summary description of data in support of the efficacy of the product in animals or in man should also be included.

Indications

The indications should be stated as specifically as possible. Liberal use should be made of the recommendations of official bodies such as the Public Health Service Advisory Committee on Immunization Practices, Center for Disease Control, the Infectious Disease Committee of the American Academy of Pediatrics, and the American Public Health Association. (Note: Subsequent to the Panel's completion of this report, the Advisory Committee on Immunization Practices was renamed as the Immunization Practices Advisory Committee and the Center for Disease Control was renamed as the Centers for Disease Control.) The specific recommendations of these advisory groups should, if appropriate, be reprinted in their entirety in the labeling. The number and frequency of injections of a given antigen(s) should be specifically stated. If products containing more or fewer antigens as combined products (e.g., DT, DTP) are preferred for a specific purpose, this should be so stated in this section. In such a case, the circumstances should also be defined when the product under consideration should be used rather than the preferred product. Where appropriate, labeling should also point out the generally accepted superiority of adsorbed vaccines and toxoids over comparable fluid products.

Contraindications

This section should state those situations in which the agent should not be used because the risk of use clearly outweighs any possible benefit. Such situations include administration of the agent to patients known to have a serious hypersensitivity to it and use of the agent in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it or not receiving the expected benefit from it. This section should list known hazards, and theoretical hazards, if mentioned, should be identified as such. The Panel encountered in its review a number of labels in which it appeared that producers were overly concerned about protecting themselves, rather than the patient.

Warnings

This section should state serious adverse reactions and potential safety hazards, limitations of use imposed by them, and steps which should be taken if they occur. This section should describe any unusual circumstances relating to the use of the product,

including particularly any circumstances under which use of the product may be hazardous or less effective. The specific circumstances and the specific hazards should be described fully.

Precautions

This section should contain the following subsections as appropriate for the product;

1. *General.* This subsection should list any special care that should be exercised to permit safe and effective use of the product by the physician.

2. *Clinical and laboratory tests.* This subsection should list those laboratory tests that may be needed to follow the patient's response or to identify possible adverse reactions.

3. *Special instructions to be given the patient.* This subsection should specify instructions for patients to achieve safe and effective use. Any patient's brochure or printed instructions to vaccines should be reprinted under this section heading.

4. *Clinically significant product interactions.* This subsection should provide specific practical guidance to the physician on avoiding and/or managing clinically significant drug interactions, such as might occur with simultaneous active-passive immunization.

5. *Pregnancy.* Recommendations concerning the use of the product during pregnancy should be detailed in this section.

Adverse Reactions

This section should contain not only a description of the nature of local and systemic adverse reactions that have been observed following use of the product as recommended, but also their relative frequency. Specific recommendations for management of adverse reactions should also be included in this section, as should recommendations for reporting of adverse reactions to the manufacturer and FDA.

Overdosage

This section should describe the signs, symptoms, and labotatory findings of accidental overdosage and the general principles of management. It should include specific information, if available, on the emergency treatment, antidotes, and the value of any recommended therapeutic measures.

Dosage and Administration

This section should state the usual recommended dose and frequency, and if appropriate, limits beyond which the product should not be administered. Precautions against inadvertent intravenous injections should be included. It should include the intervals recommended between doses, and modification of dosage needed in specific patient populations such as infants and children. Specific tables or nomograms should be included to clarify dosage schedules. This section should also contain specific directions on dilution, preparation, and administration of the product if needed, and storage conditions for stability of the product where important.

How Supplied

This section should state the available dosage forms, potencies, and units of issue of each product to which the labeling is applicable.

Generic Statement on Requirements for a Well-Controlled Field Trial

Some of the immunizing agents the Panel was required to evaluate had been tested for efficacy only in the first part of the 20th century, when the methodology for obtaining unbiased reliable results in field trials had not yet been fully worked out. Examples of such agents are diphtheria and tetanus toxoids. The respective diseases have declined in incidence, and opportunities for additional field testing for efficacy do not exist in this country.

In developing new immunizing agents, the products are generally first tested in animals for their toxicity and ability to elicit antibody response. When the animal model is suitable, the protection provided by immunization against challenge by the microorganism is also evaluated. Subequently the immune response in humans is measured, and the dose which induces a seemingly adequate immune response with an acceptable low rate of adverse reactions is sought.

The final and most important step is the field trial, when a large number of presumably nonimmune humans is inoculated, and the incidence of the disease among vaccinees and control subjects is compared.

In the past "historical" controls were frequently employed to test the effects of a new vaccine. By this no-longer-acceptable technique, the frequency of illness in a vaccinated group was compared with the frequency in a similar unvaccinated population at some time in the past. Unfortunately, a decline in disease frequency after vaccination cannot be interpreted as resulting from vaccination, because the changes may be due to natural disease cycles, to changing socioeconomic conditions, or to therapeutic measures, such as antibiotics.

Also no longer acceptable are comparisons of the frequencies of disease in those who do and do not volunteer for a vaccine study. The fallacy of this approach is that volunteers differ from nonvolunteers in many important aspects. For instance, the former may be more health conscious and inclined towards prevention; they may come from smaller families and living conditions may differ from those of nonvolunteers. Such behavioral and socioeconomic factors may affect the risk of exposure and the host's natural ability to resist infection. Modern scientific methodology requires that volunteers for a study be divided into groups by a randomization procedure, one group constituting the control group, which is given a placebo (inactive, dummy) substance. Randomization is necessary to ensure that the volunteers are distributed without bias, thereby increasing the chances that all variables, known and unknown, that might affect the results of the study are distributed evenly between vaccinated and control groups. Indeed, if the populations are heterogeneous in age, sex, race, or other important variables, it may be necessary to classify or "stratify" them into groups according to these characteristics with randomization within these groups. These rigidly designed experiments, with or without stratification, are called "controlled trials."

An additional requirement in a controlled trial is that the study be carried out double-blind if at all feasible. This implies that both the study subjects and the observers are unaware of the treatment assigned to the individual in order to ensure unbiased assessment of outcome.

Before subjects are enrolled in controlled trial, ethical considerations require that all the procedures in the studies are explained to them, and that the risks as well as possible benefits are adequately described. The right to withdraw from the study at any time without penalty is pointed out. The rights of the subjects are protected by special committees in all major research centers and by special committees at the Department of Health and Human Services. These committees review the applicable consent forms and the research. All government-sponsored research and virtually all other research involving human subjects requires review by institutional human subjects rights committees.

Whenever practical, in order to provide some benefit to the control group, a vaccine against an entirely

different disease, rather than an inactive placebo, is given to the control group.

Assignment to groups is carried out after the subjects have decided on participation, and after the study has been fully explained to them. Participation of children requires special consideration. Consent from parents as well as older children must be obtained.

In carrying out controlled field trials of new improved vaccines, ethical considerations do not allow a placebo assignment if an effective vaccine already exists. Thus, comparison can only be made between those given the new and the old product; enrollment of very large population groups may be necessary in order to distinguish small differences in efficacy.

Analysis of the results of a vaccination study is achieved by "breaking the code" identifying the allocation of individuals to vaccinated or control groups. The code is broken at the end of the study or after an outbreak of the disease has occurred. Under some circumstances it may be desirable for a statistician, who possesses the allocation code but is not participating directly in the study, to examine periodically the results as they accumulate. By this mechanism, called sequential analysis, the study can be interrupted as soon as it has become evident that one treatment or vaccine is superior to the other.

Field trials designed to measure efficacy directly have become increasingly difficult to conduct under conditions of decreasing incidence of natural disease. For this reason, serologic documentation of efficacy must increasingly be substituted in lieu of direct evidence of efficacy. The following protocol is provided to serve as an example of one type of clinical study which would provide reliable information on the efficacy of the product to be assayed as simply and as economically as possible and is illustrative of many of the concepts implicit in the Panel's position regarding well-controlled field trials as well as in FDA's regulations regarding such matters (see 21 CFR 314.111).

Sample Protocol for Assaying Efficacy of Tetanus Toxoid in Man

Objective. To determine by a study with the fewest number of subjects and fewest number of bleeds required whether a particular preparation of Tetanus Toxoid (alone or combined with Diphtheria Toxoid) produces an acceptable level of immunity in individuals not previously inoculated with Tetanus Toxoid. An acceptable level of immunity is defined as:

1. Over 80 percent of subjects having ≥0.01 International Unit of Tetanus Antitoxin per mL in a serum sample drawn 10–14 days after basic immunization (2 injections of adsorbed Toxoid or 3 of fluid Toxoid) have been given. OR

2. Over 80 percent having ≥0.1 International Unit per mL in serum sample drawn 10–14 days after a reinforcing injection given 6 to 12 months following basic immunization as defined above.

It is to be noted that 80 percent "success" by either criterion given above is a minimum tolerated level; the normal success rate, in many studies reported over the last 3 decades, is 95–100 percent.

Subjects. The study population should consist of healthy children of adults or either sex, and should have acceptable evidence of being primary responders to tetanus toxoid. In the case of infants less than 6 months of age, negative immunization history from a responsible parent or guardian would be considered acceptable. For older children and adults, the most valid evidence of primary response is the absence of serum antitoxin 7 days after the initial dose of toxoid. In neither instance is a preimmunization serum necessary. Data from older children and adult subjects screened for antitoxin negativity by a zero-day rather than a 7-day bleeding may be confounded by the inadvertent inclusion of individuals who are secondary rather than primary responders.

Numbers. Size of group should be so selected as to provide serological data on 40 acceptable subjects at end of study. Sixty is recommended as a minimum starting number if subjects can be carefully selected by good histories of no prior Tetanus Toxoid injections (about 10–20 percent will have had previous toxoid injections without their knowledge). However, larger samples, if possible, would be desirable and might provide more data. Another 10–20 percent may be expected to drop out of the study along the way.

Evaluation. On a 95 percent probability basis, US MIL–STD 105D (Canadian Standard CA–C–115; "Specification for Sampling Procedures and Tables for Inspection by Attributes," *British Standards Institution,* BS 6001, 1972), indicated that the following 2-sample sequence may be used to obtain an answer:

	Accept	Reject
1st sample of 20	1 failure	4 failures.
	for 2 or 3 failures, go to:	
2nd sample of 20 (Total of 40)	4 failures	5 failures

Active Immunization Products

Generic Statement on Diphtheria Toxoid

Diphtheria is an infectious and communicable disease of man which usually involves the upper respiratory tract and sometimes produces skin infections. The causative agent is *Corynebacterium diphtheriae,* a gram-positive bacillus with metachromatic granules. Upper respiratory diphtheria is characteristically associated with the production of pseudomembrane in the nasal passages, pharynx, and/or larynx, and with the appearance of systemic symptoms due to adsorption of an exotoxin. Fifty years ago there were approximately 200 cases per 100,000 population in the United States each year (roughly 350,000 cases annually). This has decreased to a rate of about 0.1 per 100,000 population in recent years (200 to 400 cases annually). Approximately 10 percent of patients with diphtheria succumb. Death may be due to respiratory obstruction by the memberane or to remote effects of the toxin upon the myocardium or peripheral nervous system.

Because the morbidity and mortality of diphtheria are largely a consequence of the toxin elaborated by the organism, antiserum (antitoxin) prepared by immunizing horses has been used for nearly 80 years in the treatment of the disease and for its prevention in exposed, susceptible individuals. This approach to control of the disease is only partially successful because the disease is already well established by the time it is recognized, and toxin that has been adsorbed and fixed to cells is unaffected by antitoxin.

Further, antitoxin does noting to prevent spread of disease. Penicillin or other effective antibiotic agents will usually eradicate the organism, but because they have no effect against toxin, antibiotics are only an adjunct to therapy.

Since passive immunization with antitoxin and therapy with antimicrobial agents do not provide a satisfactory approach to the control of diphtheria, active immunization of humans against the toxin has been employed for many years (also see Generic Statement on Diphtheria Antitoxin). The reduction in morbidity and mortality from diphtheria in the United States during the past half century is largely attributable to widespread immunization against the toxin.

Description

Diphtheria toxoid is a cell-free

preparation of diphtheria toxin treated with formaldehyde so that when administered to humans it does not produce the known toxic effects of diphtheria toxin, but nonetheless produces a specific immune response to the toxin.

The rationale for this preparation is based on the fact that the pathogenicity of the *Corynebacterium diphtheriae* for man is almost entirely derived from the effects of its exotoxin. Rarely, apparently nontoxin producing strains of the organism produce disease. Also uncommon is disease produced by toxigenic strains in individuals immune to the toxin. In these rare instances, the significance of the disease is dependent upon local inflammatory response, and not upon systemic dissemination of toxic products.

Early in this century, attempts were made to devise means by which immunity to the toxin might be induced in man. The potency of the toxin is such that the miniscule amounts that can be safely administered to man fail to induce protection. Indeed, the disease itself sometimes fails to induce immunity in survivors. The first successful preparation for inducing immunity was a balanced combination of diphtheria equine antitoxin and the toxin. Disadvantages included reversion to toxicity when frozen, frequent sensitization to horse serum, and less than optimum induction of the immune state.

Attempts to detoxify the toxin without destroying its antigenicity repeatedly failed because of the instability of the toxoid, until it was shown that formaldehyde treatment of the toxin produced the desired result. Current toxoids are a result of this observation.

Combinations of the formaldehyde-inactivated toxoid with various aluminum compounds have resulted in preparations more antigenic than the fluid (plain) toxoid, and represent the most commonly used preparations in the United States. Such preparations are designated "adsorbed."

Production

A strain or *Corynebacterium diphtheriae* established as a potent toxin producer is grown in a liquid medium so constituted as to afford optimum conditions for toxin production. The medium must be free of blood products, horse or other animal serum, and any proteins known to be allergenic to man. Removal of bacterial cells and sterilization are accomplished by centrifugation and filtration. The resultant toxin is tested for potency according to the U.S. standards and is incubated with formaldehyde in established proportions to effect conversion to toxoid. Before or after conversion to toxoid, additional steps are usually taken to purify and concentrate the fluid antigen partially.

Treatment of the fluid toxoid with aluminum compounds is employed utilizing established techniques to produce the adsorbed product. A preservative (usually thimerosal but never phenol) is added.

The amounts of toxoid present in preparations are specified in flocculation units (Lf), measured by established techniques.

Use and Contraindications

This product, used for active immunization against diphtheria, is rarely indicated as a single toxoid, either in the fluid or adsorbed form. For primary immunization of children younger than 7 years of age, it should almost always be used in a combined product with tetanus toxoid and pertussis vaccine. Poliomyelitis vaccine consisting of inactivated poliovirus may be included as a fourth antigen, but live, oral, poliovirus vaccine consisting of attenuated virus is currently preferred for poliomyelitis immunization in the United States. The triple antigen products are preferred over monovalent diphtheria toxoid not only because of efficiency and economy but also because pertussis vaccine enhances the immunogenicity of the toxoids (adjuvant effect). Also, the adsorbed products are more antigenic than the fluid products and the antitoxic immunity is of longer duration.

Thus, it is strongly recommended that routine immunization of children under 7 years of age against diphtheria be accomplished by the use of combined adsorbed diptheria and tetanus toxoids and pertussis vaccine (DTP), according to schedules recommended by the Public Health Service Advisory Committee on Immunization Practices of the United States Public Health Service, the American Academy of Pediatrics, and the American Public Health Association. These advisory bodies also recommended the use of adsorbed combined tetanus and diphtheria toxoids of the adult type (Td) for primary immunization of children older than 6 years and adults. However, the efficacy of Td as a primary immunizing agent against diptheria has not been firmly established. (See Special Problems, Number 1, diphtheria toxoid generic statement.)

In the unusual instances in which primary immunizatin with monovalent diphtheria toxoid is indicated, the adsorbed form is preferable. Primary immunization with adsorded toxoid comprises three doses, 2 given 4 to 8 weeks apart, and the third dose (reinforcing) 1 year later. Booster doses should probably be given 5 years after the primary three doses and again after an interval of approximately 10 years. (See Special Problems, Number 1, diphtheria toxoid generic statement.) In children older than 6 yeas and adults the booster doses should probably be given as one-fifth of the usual dose or as Td because of an increased likelihood of reactions. Monovalent diphtheria toxoid may be used for booster doses in the presence of an outbreak of diphtheria, but usually under these circumstances advantage should be taken of the opportunity to enhance tetanus immunity by the use of Td.

If the fluid toxoid is used, primary immunization should include 4 doses, 3 doses 4 to 8 weeks apart, and a fourth dose 1 year later. Booster doses should be given as with the adsorbed preparation.

The fluid toxoid may be administered subsutaneously or intramuscularly. The adsorbed toxoid is preferably administered intramuscularly.

Absolute contraindications to the use of diphtheria toxoid are virtually nonexistent. Apparent anaphylactic reactions to diphtheria toxoid have been rarely reported. A marked fibrile response to an injection should be cause for reducing the subsequent dose to one-tenth or one-fifth the former dose. Individuals receiving corticosteriods or other immunosuppressive drugs may not display an optimum immunologic response; accordingly, if discontinuation of such drugs is anticipated within the immediate future, immunization should be delayed until that time. In the presence of a fibrile illness it is advisable not to administer diphtheria toxoid alone or in combination with pertussis vaccaine because of possible confusion as to the cause of further fever.

Inasmuch as clinical diphtheria may not induce adequate active immunity, immunizationof individuals who have recovered from diphtheria and who remain Schick-test positive should be undertaken employing a reduced initial dose because of possible sensitivity.

Safety

Fluid and adsorbed diphtheria toxoid must be tested to ensure sterility, the absence of free toxin, and the absence of blood group substances in significant

amount. All of these tests are well defined and described by the Bureau of Biologics. Experience with the administration of millions of doses has shown that life-threatening reactions to this toxiod are extremely rare. Transient local reactions and systemic symptoms, primarily fever, are frequent, expecially in individuals sensitized by prior exposure to the toxin or toxoid. These reactions are not life-endangering and usually persist only a day or two. The severity of these reactions is directly proportionate to the amount of toxoid administered.

Manufacturers are required to record all reported reactions.

Efficacy

Although controlled studies employing currently acceptable design methodology and statistical analysis have not been carried out, extensive experience in many countries has shown that the systematic use of this product for the immunizatin of infants and children has been associated with a striking reduction in the incidence of the disease. Similar but less extensive experience indicates comparable effectiveness in older age groups.

The potency of diphtheria toxoid prior to administration to humans is tested in guinea pigs, and standard procedures for such testing have been developed and are required of manufacturers by the Bureau of Biologics. In the case of the fluid toxoid, each lot must be tested by immunizing guinea pigs, followed by subsequent challenge with toxin to show protection. Unimmunized control animals must be employed to ensure the lethality of the toxin used to challenge the immunized animals. Adsorbed diphtheria toxoid is tested by immunizing guinea pigs and subsequently determining diphtheria antitoxin levels as prescribed.

Quantitative correlation, however, between the results of animal protection tests and primary immunogenicity in man has not been established, although it is assumed that there is a direct relationship. For primary immunization, direct testing of antitoxin response in man should be required, and should be repeated whenever significant changes in the manufacturing process are made. However, past experience indicates that all toxids which meet the requirements of the Office of Biologics Research and Review (OBRR) for potency in animals have proved effective as boosters in man. (See Special Problems, Number 3, Diphtheria Toxoid Generic Statement.)

Because field testing of disease prevention is currently not feasibile, testing for efficacy in man requires evaluation of the induction of serologic immunity. This may be achieved by serological tests, or by the performance of the Schick skin test which reflects serologic and clinical immunity with satisfactory accuracy. Three doses of the fluid toxoid, given 4 weeks apart, or 2 doses of the adsorbed preparation, separated by 4 weeks, should result in at least 80 percent conversion of Schick positive or seronegative subjects to the Schick negative state of to seropositivity (0.01 or more units of dophtheria antitoxin per mL of serum) by 1 month after the last dose. To avoid confounding by anamnestic responses, use of the Schick test technique for efficacy testing in man should be limited to young infants clearly receiving primary immunization. Similarily, infants should be used for serologic testing, or a blood sample should be drawn 7 days after the first dose and tested for evidence of an accelerated immune response which, if absent, would indicate primary immunization.

Special Problems

Diptheria toxoid, as an immunizing agent in man, presents several problems that warrant efforts toward solution.

1. Although the safety of different lots of diptheria toxoid products may be assured by animal testing, no aninal model or other laboratory technique for evaluation of effectiveness has been directly coorelated with primary immunogenicity in human with acceptable precision. Titers of antibodies as determined by neutralization of the toxin in experimental animals or in tissue culture systems are better related to immunity than is the presence of hemagylutinating antibodies in serum specimens. However, the presence of low neutralizing titers does not ensure protection against large amounts of toxin.

2. The nonspecific reactogenicity of diphtheria toxoid, probably due largely to extraneous proteins derived from the organisms, represents a complicating factor in the immunization of individuals who have become sensitized to these proteins. The Panel has noted that there are no purity requirements in terms of Lf content per milligram of nitrogen except for the Td product.

3. For several reasons, diphtheria toxoid, fluid or adsorbed, is not as effective an immunizing agent as might be anticipated. First, clinical diptheria may occur occasionally in immunized individuals—even those whose immunization is reported is reported as complete by recommended regimens. However, when it does occur in such individuals, it appears to be milder. Second, diptheria toxoid provides protection only against the toxin and not against the somatic components of Corynebacterium diphtheriae. Occasional local infections, respiratory or cutaneous, may occur in immune individuals and nontoxigenci strains may produce focal infections. Although both of these situations are encountered from time-to-time, they are not of major importance. Third, the permanence of immunity induced by the toxoid in the light of decreasing likelihood of exposure to the organism (the "streetcar booster") is open to question. In the absence of occasional exposure, it is possible that individuals immunixzed as children will not retain a degree of immunity that will provide adequate protection in later years. Fourth, the smaller amount of diphtheria toxoid present in tetanus and diphtheria toxoids combined for adult use (Td) has never shown conclusively to be an adequate primary immunizing agent. Furthermore, the intervals between booster doses of Td in adults sufficient to maintain diphtheria immunity have not be established. Fifth, commendable efforts by producers to reduce the nonspecific reactivity of the toxoid by increased purification may have resulted in diminished immunogenicity.

Finally, the absence of proof recently obtained in humans for certain diphtheria toxoids by simple serological tests or readily measureable antibodies could not allow a Category I assignment. (See section 2.b. (2) of the Introduction in this Report.)

Recommendations

The following recommendations for the production, use, and evaluation of diphtheria toxoid are made:

1. Of maximum importance is the development of an animal or laboratory testing system that correlates consistently and with acceptable precision with primary immunogenicity in humans. Public funding to support such research should be made available. Until such a model is established, current toxoids and new variations on such toxoids will require field testing in humans employing serologic methods. Such field testing is expensive and difficult to conduct both because of the problem of finding suitable nonimmune subjects and because of the current restraints on research using human beings. Further, the necessity for field testing of each toxoid produced by a new or varied technique would understandably inhibit manufacture·s in terms of innovation and improvement, and place a difficult burden upon the Bureau of Biologics in determining which alterations in production methods